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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/657,811	09/08/2003	Mark Ledeboer	VPI/02-121 US	1126

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VERTEX PHARMACEUTICALS INC.
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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/657,811	LEDEBOER ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,8-10 and 15-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,8-10 and 15-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *February 16, 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted February 16, 2007 wherein claims 1, 15-18, 20, 21, and 23 are amended and claims 2-4, 7, and 11-14 are cancelled. This application claims benefit of provisional application 60/408813, filed September 6, 2002.

Claims 1, 5, 6, 8-10, and 15-23 are pending in this application.

Claims 1, 5, 6, 8-10, and 15-23 as amended are examined on the merits herein.

Applicant's amendment, submitted February 16, 2007, with respect to the rejection of instant claims 1-17 and 19-23 under 35 USC 112 for indefiniteness for reciting the indefinite terminology, "substituted or unsubstituted cycloalkyl," has been fully considered and found to be persuasive to remove the rejection as the base claim 1 no longer recites this phrase. Therefore the rejection is withdrawn.

Applicant's amendment, submitted February 16, 2007, with respect to the rejection of instant claims 20, 21, and 23 under 35 USC 112 for lacking enablement for treating neurodegenerative, neurological, or immunological disorders, has been fully considered and found to be persuasive to remove the rejection as the claims as amended are drawn only to the treatment of ischemic and inflammatory neurological disorders and compositions for the treatment of stroke. Therefore the rejection is withdrawn.

Applicant's amendment, submitted February 16, 2007, necessitates the following new grounds of rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's amendment submitted January 8, 2007 with respect to the aforementioned claims has been fully considered and but is deemed to insert **new matter** into the claims since the specification as originally filed does not provide support for a method of treating an ischemic or inflammatory disorder **of the central nervous system**. Although the specification as originally filed does mention specific disorders such as stroke that affect the central nervous system, nowhere does it recite any general teaching that the claimed invention is useful for treating **all ischemic or inflammatory disorders of the central nervous system**. As the instant specification as filed contains no description of this particular limitation that the disorder be a disorder of the central nervous system the specification as originally filed does not provide support for the subject matter of instant claims 21-23. See *in re*

Smith, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). Because Applicant's amendment necessitated this new ground of rejection, the rejection is made **FINAL**.

The following rejections, of record in the previous office action, are maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, 6, 8-10, and 15-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (PCT international publication WO01/12621, of record in the previous office action) in view of Silverman. (Reference of record in the previous office action) Green et al. discloses a number of isoxazole compounds of a general structure given on p. 14. (lines 18-30, formula **IA**) The broad limitations of formula **IA** disclosed in Green et al. include embodiments where the groups R^2, and G are CH_2(heterocyclyl) and aryl, respectively, and Q is 2-aminopyrimidine, as disclosed in formula **I** of instant claim 1. Specific embodiments of the compounds of Green et al. include those in which G is phenyl or 4-fluorophenyl, Q is 2-aminopyrimidine, R^2 is cyclohexyl or 4-cyclohexanol, and R^2 is CH_2(piperidinyl). (p. 31, examples XIA-39 – XIA-53) Green et al. also discloses that these compounds are useful for the treatment of a number of disorders including inflammatory diseases and reperfusion/ischemia in stroke, heart attacks, and organ hypoxia. (p. 7, lines 15 – p. 8, line 7) Green et al.

discloses that a pharmaceutical composition involving these active agents may additionally comprise a pharmaceutically acceptable carrier. (p. 50, lines 1-16) Green et al. further discloses that these compounds may be combined or administered concurrently with additional active agents which are normally administered to treat the condition being treated. (p. 55, lines 9-16) Green et al. does not explicitly disclose the specific compounds of instant claims 1, 2, and 4-18, or the pharmaceutical compositions and methods of instant claims 19-23. Green et al. also does not explicitly disclose a combination of the claimed compounds with therapeutic agents having any of the indications recited by instant claims 20 and 23.

Silverman discloses that the substitution of certain equivalent functional groups, or bioisosteres, in an existing molecule, produces derivatives having similar biological properties. (p. 19, under the heading, "Bioisosterism") In particular, Silverman discloses that rings containing –O-, -S-, -CH_2, or –NH- groups are bioisosteres. (p. 19, table 2.2, no. 5) Therefore compounds containing piperazine, piperidine, and morpholine rings are expected to possess similar biological properties.

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce the compounds of formula I disclosed in instant claim 1, and their variants disclosed in instant claims 2 and 4-18. It would also have been obvious to one of ordinary skill in the art to prepare the pharmaceutical compositions of instant claims 19-20 and to use them in the methods of instant claims 21-23. It would also have been obvious to make a pharmaceutical composition comprising a compound of formula I and an additional therapeutic agent as described in instant claims 20 and 23, and to co-

administer the compound of formula **I** and the additional agent as described by instant claim 23.

One of ordinary skill in the art would have been motivated to prepare the compounds of instant claims 1, 2, and 4-18 because these compounds fall within the limitations of the structures disclosed by Green et al., and additionally because the specific functional groups defined in these claims are all disclosed in various embodiments of Green et al., particularly examples XIA-39 – XIA-53. In particular, in view of Silverman's teaching that –O-, -S-, -CH_2, or –NH- groups are bioisosteric when appearing in rings, one of ordinary skill in the art would have been motivated to prepare bioisosteres of the disclosed compounds of Green et al., including the compounds of the claimed invention. One of ordinary skill in the art would have been motivated to prepare the pharmaceutical compositions of instant claims 19-20 and practice the methods of claims 21-23 because Green et al. discloses that the compounds of formula **IA** are useful for treating inflammatory diseases and ischemia. Additionally, one of ordinary skill in the art would have been motivated to practice these compositions and methods with additional active agents, particularly an anti-inflammatory agent, an anti-asthma agent, or a treatment for stroke, as claimed by instant claims 20 and 23 because these additional components are appropriate therapeutics for the disorder being treated, and because Green et al. discloses that the related compounds of Green et al. may be administered along with additional therapeutic agents appropriate to the disorder being treated.

One of ordinary skill in the art would reasonably have expected success in preparing the compounds of instant claims 1, 2, and 4-18 because these compounds fall within the limitations of formula **IA** of Green et al. and are substantially similar to various embodiments disclosed by Green et al. One of ordinary skill in the art would have reasonably expected success in practicing the therapeutic compositions and methods of instant claims 19-23 because these compositions and methods are directed toward the treatment of diseases which the claimed compounds are already known to be useful for treating. Furthermore, it has been held that it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to practice a third composition for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's argument, submitted February 16, 2007, with respect to the above rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that because Green et al. does not disclose any compounds that fall within the claimed genus. However, as stated above, one of ordinary skill in the art would have been motivated to produce the claimed compounds, which are included within the generic structure I on p. 8, lines 10-20 and p. 14, lines 20-30 of Green et al., with the expectation that they are so structurally similar to the specific embodiments taught by Green et al. as to have the same biological properties and utility.

Furthermore, Applicant argues that the claimed compounds unexpectedly exhibit increased anti-ischemic potency and anti-inflammatory activity. However, the similar compounds of Green et al. are already disclosed by Green et al. to be useful for the treatment of ischemia and inflammatory diseases. Applicant discloses no data that would indicate that the anti-inflammatory and anti-ischemic activity of the claimed compounds is greater than what would be expected from the teaching of Green et al. Applicant claims that these compounds possess improved properties but does not provide any data comparing them directly to the prior art JNK inhibitor compounds. Therefore they cannot be said to be unexpectedly improved over the prior art.

Therefore the rejection is deemed proper and made **FINAL**.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5, 6, 8-10, 15-19, and 21-22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6693108 (Reference of record in previous office action, herein referred to as '108) in view of Silverman. (Reference of record in previous office action) Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds included within the structure of formula I of instant claim 1 fall within the limitations of the species claimed in claims 1-11 of '108. Claims 1-6 of '108 claims a number of isoxazole compounds of a general structure which includes embodiments where the groups R^2, and G are CH_2(heterocyclyl) and aryl, respectively, and Q is 2-aminopyrimidine, as disclosed in formula I of instant claim 1. Claim 7 of '108 claims specific embodiments of this structure, including those in which G is phenyl or 4-fluorophenyl, Q is 2-aminopyrimidine, R^2 is cyclohexyl or 4-cyclohexanol, and R^2 is CH_2(piperidinyl). (Examples XIA-39 – XIA-53) Claim 8 0f '108 discloses a pharmaceutical composition comprising any of the compounds of claims 1-7 of '108 and a pharmaceutically acceptable carrier, as claimed in instant claim 19. Claims 9-11 of '108 claim methods of using these compounds to treat various diseases, including inflammatory diseases and ischemia. Claims 1-11 of '108 do not explicitly disclose the specific compounds of instant claims 1, 2, and 4-18, or the pharmaceutical compositions and methods of instant claims 19-23.

Silverman discloses that the substitution of certain equivalent functional groups, or bioisosteres, in an existing molecule, produces derivatives having similar biological properties. (p. 19, under the heading, "Bioisosterism") In particular, Silverman discloses that rings containing –O-, -S-, -CH_2, or –NH- groups are bioisosteres. (p. 19, table 2.2, no. 5) Therefore compounds containing piperazine, piperidine, and morpholine rings are expected to possess similar biological properties.

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce the compounds of formula I disclosed in instant claim 1, and their variants disclosed in instant claims 2 and 4-18. It would also have been obvious to one of ordinary skill in the art to prepare the pharmaceutical compositions of instant claims 19-20 and to use them in the methods of instant claims 21-23.

One of ordinary skill in the art would have been motivated to prepare the compounds of instant claims 1, 2, and 4-18 because these compounds fall within the limitations of the structures disclosed by claims 1-6 of '108, and additionally because the specific functional groups defined in these claims are all disclosed in various embodiments of claim 7 of '108, particularly examples XIA-39 – XIA-53. In particular, in view of Silverman's teaching that –O-, -S-, -CH_2, or –NH- groups are bioisosteric when appearing in rings, one of ordinary skill in the art would have been motivated to prepare bioisosteres of the disclosed compounds of claim 7 of '108, including the compounds of the claimed invention. One of ordinary skill in the art would have been motivated to prepare the pharmaceutical compositions of instant claim 19 and practice the methods of claims 21-22 because claims 9-11 of '108 are directed toward methods of using these

compounds for the treatment of disorders including inflammatory diseases and ischemia.

One of ordinary skill in the art would reasonably have expected success in preparing the compounds of instant claims 1, 2, and 4-18 because these compounds fall within the limitations of formula **IA** of claims 1-6 of '108 and are substantially similar to various embodiments disclosed by claim 7 of '108. One of ordinary skill in the art would have reasonably expected success in practicing the therapeutic compositions and methods of instant claims 19-23 because these compositions and methods are directed toward the treatment of diseases which the claimed compounds are already known to be useful for treating and which are clamed by claims 9-11 of '108.

Response to Argument: Applicant's argument, submitted February 16, 2007, with respect to the above rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are identical to those made with respect to the above rejection under 25 USC 103, and are found unpersuasive for the same reasons.

Therefore the rejection is deemed proper and made **FINAL**.

Summary

No claims are allowed in this application. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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